# Building Quality Data

Center for
Veterinary Medicine

June 4 and 6, 2013

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# Data Quality Webinar

- Final workshop of 10 required by Animal Drug User Fee Authorization Act of 2008
- Workshop series has been useful to address issues of mutual concern
  - Antimicrobial drugs for companion animals
  - Manufacturing Chemistry QbR process for sterile process validation
  - Medicated Feeds

# Why High Quality Data?

- Short answer – faster drug approvals
- Each data point is becoming more valuable
  - CVM is working to minimize the number of studies
  - Reducing animal numbers and data collected in the remaining studies
- Smoother review process

# Smoother Review Process

- Easily reconstruct the study
- Determine the data were collected appropriately
- Permit efficient analysis of study results
  - Statistical and scientific
- Confirm adherence to ‘requirements’
  - Laws, regulations, guidance, policies

# Webinar Development

- AHI and CVM held a series of meetings to discuss issues related to lifespan of high quality data for target animal safety and clinical effectiveness studies:
  - From conceptualization of the need for data to submitting that data to CVM

# Results of Those Discussions

- Identified five critical areas where improvements would be most effective
  - Study protocol development
  - “Prior to Live” and “Live” phases of study conduct
  - Reporting of study results
  - Submitting results/data to CVM

# Scope of this Webinar

- Is not an exhaustive examination of all possible actions that can improve the quality of data
- Is the identification and discussion of those actions that are most likely to have a noticeable impact on data quality

# Thank You!

- We believe that putting the actions described during the webinar into routine practice can have a favorable impact on the quality of data submitted to CVM and, thus, the drug approval process

# Building Quality Data - Protocol Development

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# Protocol Development

- Objective
  - Good protocol design aids in collection of accurate, complete, precise and orderly data
  - CVM's standards for quality data
    - Build into protocol
    - Assure appropriate data collected/analyzed
  - Share with industry best practices to assure timely submission review

# Topics

- Pre-submission Conference and other meetings
- Sponsor Review
- Overall Study Design
- Randomization
- Masking
- Adverse Events
- Inclusion/Exclusion
- Removal of Animals
- Endpoints-Choice, Measurement, and Timing
- Data Analysis
- Data Capture Forms
- Protocol Training
- SOPs

# Protocol Concurrence

- General reminder that protocol concurrence is not required but helps to assure that studies are adequate to support drug approval

# Pre-submission Conference (PSC)

- 30+ days beyond receipt of meeting request
- CVM uses time for internal meetings to review meeting materials
- Sponsor should define indication and pivotal endpoints
- Discussion of possible label language

# Pre-submission Conference

- Opportunity for sponsor to propose development plan and general pivotal study designs
- Sponsor can provide data summaries to support key protocol designs
- Memorandum of Conference summarizes key points and agreements made during the meeting-contact CVM if have questions

# Pre-submission Conference

- Early Information Option
  - Sponsor can provide preliminary data, (e.g. pilot studies, PK studies) approximately 100 days prior to the pre-submission conference to allow CVM to review the data and provide more detailed discussion of pivotal studies during meeting
  - Goal is for sponsors to submit protocol(s) immediately after pre-submission conference

# Protocol Development

- Resources
  - Guidance For Industry #85, #185, and #215
  - Study specific guidances, e.g. species specific anthelmintic guidances
  - 21 CFR Part 58 for GLP studies
  - AHI Points to Consider- helpful, but has some outdated procedures (e.g. no End Review Amendment or eSubmitter procedures )

# Protocol Development Meeting(s)

- Sponsor may request meeting(s) after PSC to discuss specific protocol issues in more detail
- Especially important for novel products, indications, or complex study designs
- Allows CVM to provide specific feedback
- May not be necessary if sufficient early information provided prior to PSC

# Internal Review of Protocol by Sponsor

- Internal sponsor review of protocols is critical
- Input from statisticians, consultants, investigators, and monitors may improve quality and avoid mistakes
- Quality Assurance (QA) group can help by reviewing protocol as well

# Drafting the Protocol

- Identify the data capture forms (DCFs) in the text either by title or number
- Describe procedures consistently from one section to the next, e.g. use the same terminology
- Organize and number sections to help investigator find information quickly

# Overall Study Design

- Sponsor shouldn't base protocol only on FOIs because CVM's current thinking may have evolved
- Sponsor should review protocols from third parties to confirm that protocol and DCFs are acceptable
- Specify pivotal and supportive variables to support proposed indication or safety

# Overall Study Design

- Describe experimental design e.g. parallel, cross-over, and any blocking or stratification
- Describe treatment groups, e.g. control groups
- Describe sample size for study and treatment allocation, e.g. 1:1, 2:1, etc.

# Randomization

- Provide enough detail to illustrate the implementation and randomization restrictions such as blocking, stratification, or unequal treatment allocation (e.g. 2:1 treated to placebo)
- Protocol should specify that all details of randomization will be included in the FSR

# Randomization

- Describe who will perform the randomization and how it will be implemented at study site, e.g. generated for each site prior to study initiation or generated centrally in real-time
- If the study is masked, the treatment information should not be disclosed on the randomization sheet

# Masking

- For this webinar, masking includes both masking of treatment and personnel
- Masking is important for reducing observer bias and  should be appropriate to the bias control needed for the study

# Masking

- It is important to maintain separation of function between masked and unmasked personnel throughout the study
- Specify the masking status of all key personnel, e.g. sponsor, study director, monitor, treatment administrator, statistician, or owner

# Masking

- Ensure that  personnel making observations are not aware of the treatments
- Personnel managing real-time data should remain masked throughout the study, e.g. statistician, Clinical Investigator, or Study Director

# Masking

- Use more labels/codes than the actual number of groups
  - In a study with 2 treatment groups with equal allocation, use at least 4 treatment codes (e.g. A/B/C/D).
  - In unequal allocation, it is important that you use at least 3 (e.g. A/B/C)

# Masking

- Specify conditions under which unmasking is allowed (e.g. serious adverse events or human exposure) and how masking will be protected for remaining subjects
- Pay particular attention to protecting study integrity for interim analysis, e.g. a separate statistician to perform interim calculations

# Masking

- Describe timing and process for unmasking the study, e.g. after data locking

# Adverse Events (AE)

- AE defined in the GCP guidance, GFI #85
- Serious AE may be defined if protocol states to notify sponsor or monitor in case of SAEs
- Train investigators to report AEs even if appear to be unrelated to treatment or are common diseases for that species or class of animal

# Adverse Events

- A list of common terminology for investigators to use makes reporting easier
- State when to report AEs (e.g. specific time frame) and to whom (e.g. monitor)
- Dedicated DCFs make reporting easier

# Adverse Events

- Multiple DCFs may be helpful to track progress and resolution of AEs (e.g. follow-up forms)
- DCFs- include date of occurrence, date recorded, animal ID, pen ID, signs, treatment of AE (including concomitant meds), and date of resolution

# Adverse Events

- AE DCFs should be designed not to compromise masking unless unmasking is necessary to treat animal
- Monitors should check for AEs in other sources, such as medical records and owners' diaries

# Removal of Animals

- The following should be described clearly in the protocol
  - Criteria for removal
  - Procedures and documentation
  - Whom to contact in case of removal
  - How removed animals will be accounted for in the effectiveness and safety analyses

# Inclusion/Exclusion

- Chosen criteria depend on type of study and pivotal variables
- May include reasonable diagnostics to ensure eligibility
- List exclusionary medications, physiological conditions, and/or diseases

# Inclusion/Exclusion

- Consider criteria carefully so they are appropriately restrictive or expansive as necessary to ensure suitable candidates
- Final labeling should be considered

# Choice of Variables and Endpoints

- Should be consistent with proposed indication
- Should be measurable in a meaningful way
- Should be discussed during protocol development if new endpoint
- Early information may be beneficial to justify endpoint and when to assess

# Measurement of Variables and Endpoints

- Methodology and procedures should be
  - Well-defined
  - Accurate
  - Reproducible
- If used, equipment must be properly calibrated
- Consider contacting CVM if planning to use a new methodology

# Timing of Variables and Endpoints

- Dependent on indication, e.g. early vs. late stages of disease
- Dependent of type of outcome, e.g. complete vs. partial response
- May be dependent on drug levels in some cases, e.g. antimicrobials

# Data Analysis

- Include hypothesis to be tested
- Pivotal analysis should match the primary clinical hypothesis
- Describe treatment effect(s) to be estimated
- Specify significance threshold
- Define experimental unit

# Data Analysis

- Describe the principal features of the proposed pivotal analysis of the effectiveness variables
  - Statistical model, including fixed/random design factors that reflect any randomization restrictions
  - Analysis details (e.g. covariance structures)
  - Plan for unexpected analysis problems (e.g., missing data, non-convergence issues)

# Data Analysis

- Prospectively define outcomes for animals removed prior to final endpoint measurement, e.g. drug-related AE = failure or withdrawals unrelated to treatment = unevaluable

# Interim Analysis

- State purpose of interim analysis, e.g. sample size calculations, stopping for futility or remarkable effectiveness
- Describe personnel involved and how study masking will be maintained
- State when the planned analysis will occur, e.g. based on time, number of subjects, etc.

# Interim Analysis

- Describe the process which includes data freezing, which data will be analyzed, what type of analysis will be performed, and plan for including frozen dataset in final submission
- Describe any implications on final analysis, e.g. alpha adjustment

# Data Management

- Describe timing and process for data freeze and data lock (e.g. data audits, QC process)
- Locked database considered electronic raw data
- Any variable transformations or computations, e.g. unit conversion, should be planned for after data lock

# Data Management

- Entire electronic raw dataset should be included in the submission, not the subset of data that was analyzed

# Data Capture Forms (DCFs)

- DCFs that capture primary variable data should be included with protocol for concurrence
- Design DCFs from investigator's perspective to minimize errors
- Understand how the DCFs will be used to ensure that the they accurately capture the critical information

# Data Capture Forms

- Some sponsors have DCF databanks where generic forms are modified for specific studies
- Training investigators how to use DCFs is most effective way to minimize errors; consider a “dry run” to test DCFs
- Involve QA in the design and review of DCFs

# Data Capture Forms

- Provide enough space for necessary information
- Comments made by laypeople may need more space
- Provide guidance on type of comments to add in allotted space
- Provide signature/initials space for observers and recorders if applicable

# Data Capture Forms

- Most DCFs include animal ID, date of documentation, and initials or signatures of study participants
- Be aware of bias concerns; use a different form for each day rather than track data over time on a single form
- Do not include treatment group on forms used by masked personnel

# Data Capture Forms

- CVM reviews DCFs to see if they collect appropriate information and preserve masking
- CVM provides comments on DCF deficiencies
- Numbering or titling DCFs and referring to them in the protocol helps the study participants and facilitates protocol review

# Data Capture Forms: GLP vs GCP

- Greater variation in DCFs used for field studies
- Sponsor should review DCFs provided by CROs or third party to see if acceptable
- For GLP studies, the site often has its own forms, so may be reluctant to use sponsor’s forms

# Electronic Data Capture Forms

- Two main types
  - GLP
    - Toxicology study systems, e.g. Provantis, Xybion systems
  - GCP
    - Form based system where electronic DCFs mimic paper forms and data collection methods used in field studies

# Electronic Data Capture Forms

- Must be 21 CFR Part 11 compliant
- Part 11 issues
  - Validation of software
  - Signatures-what are considered valid
  - Inclusion of audit trail to use for monitoring
- Sponsor may want to introduce CVM to proposed software in a presentation

# Protocol Training

- Most effective and cost efficient way to minimize errors and maximize consistency
- Gives personnel a chance to point out problems with protocol or DCFs
- Have investigator or personnel complete forms using mock data to debug forms
- Provide principles for rounding numbers when recording data or dosing drug

# Protocol SOPs

- For both GLP and GCP studies, SOPs may not be necessary if procedures are described adequately in text
- For both GLP and GCP studies, SOPs critical to the protocol (i.e. pertain to assessment of primary variable) should be submitted with the protocol for review
- Sponsor may wish to discuss which SOPs are considered critical before submitting protocol

# Protocol SOPs

- In some cases ( both GLP and GCP studies), procedures such as microbiological assays (or other procedures as appropriate) can be submitted separately for review; sponsors should  talk to the review division if they want to do this

# Protocol SOPs

- GCP studies
  - SOPs not required by CFR as part of protocol but may be used to support assessment of primary variable or Part 11 validation
- GLP studies
  - Minimum of 12 critical areas required by 21 CFR Part 58 have to be addressed in SOPs or in the protocol text

# Protocol SOPs

- GLP studies
  - Sponsor should ensure that all sites able to meet SOP requirements
  - Some SOPs may be considered proprietary by CRO or electronic data collection vendor, so sponsor can reference a submission outside of the protocol, such as a Veterinary Master File

# Summary

- Topics chosen for presentation are the areas where it is important to build quality into the protocol
- The suggestions made today are based on feedback from both CVM reviewers and sponsors
- A well-written protocol decreases the potential for mistakes and increases the chance of a one-cycle review

# Building Quality Data – Prior to Live and Live Phases

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June 4 and 6, 2013

# Prior to Live and Live Phase

- Selection of sites and investigators
- Training of personnel
- Implementation of protocol
- Data collection and management

# Outline of Topics

- Site Selection
- **Personnel Training**
- Test and Control Articles
- Feed and Water
- Concurrent Medications
- Test Animals
- Control of Bias
- Data Collection and Management
- Amendments and Deviations
- Adverse Events
- Quality Oversight

# Site Selection

- Selection of Clinical Investigator (GCP) or Study Director (GLP)
- Facility considerations
- Personnel qualifications
- GLP specific concerns

# Selection of Clinical Investigator (GCP) or Study Director (GLP)

- Clinical investigator
  - Sufficient knowledge, scientific training, and experience
  - Inspectional history
  - Able to fulfill responsibilities of protocol and applicable regulations and guidelines

# Selection of Clinical Investigator (GCP) or Study Director (GLP)

- Study Director
  - Able to fulfill responsibilities required by GLP regulations (21 CFR 58.33)
    - Responsibilities outlined in 21 CFR 58.33 are separate from those of the test facility management and QA unit
  - Appropriate education, training, and experience

# Facility Considerations

- Geographic location
- Schedule
- Contract laboratories
- Inspectional history
  - Has the site been inspected?
  - If an FDA Form 483 was issued, were the issues resolved?
- Animal Housing and Handling

# Facility Considerations

- Standard operating procedures
  - Protocol specified procedures take precedence
- Equipment
  - Meets needs of protocol
  - Maintenance and calibration
  - Ensure scale checks/scale verifications are performed and recorded properly

# Facility Considerations

- Is there appropriate storage available for the drug products?
  - Storage temperatures
  - Security
- Data handling and storage
  - Are archiving procedures adequate?
  - If electronic data capture used, are they 21 CFR Part 11 compliant?

# Personnel Qualifications

- Sufficient to ensure compliance with protocol and regulations
- Substantial evidence of effectiveness (21 CFR 514.4)
  - …studies conducted by experts qualified by scientific training and experience
- GLP:  21 CFR 58.29
  - … each individual shall have education, training, and experience, or combination.. and testing facility must maintain current summary of training and experience and job description

# GLP Questions for Site Selection

- Does the site have the appropriate organizational structure and sufficient personnel?
  - Test facility management, study director, QA unit, and other supporting personnel
- Are facilities sufficient to allow for proper study conduct?
  - 21 CFR 58 Subpart C and E

# GLP Questions for Site Selection

- Do they have appropriate equipment of adequate capacity; suitably located; maintained and calibrated?
  - 21 CFR 58 Subpart D
- Does the site have adequate Standard Operating Procedures which are kept up to date?
  - Minimum SOPs listed in 21 CFR 58.81

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# Personnel Training

- May include training on GCP/GLP
- Overall protocol training
- Protocol procedure specific training
  - Particularly for critical data collection, new or difficult procedures
- Training on data capture forms
  - Training using mock data often helpful
- Documentation of all training is essential

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# Test and Control Articles

- Consider timing of study in relation to Chemistry, Manufacturing, and Controls (CMC) technical section
  - Stability testing
  - Assay method validation
- Identification and accountability
  - Labeling of drug products (e.g. investigational labeling in 21 CFR 511.1)
- Storage

# Test and Control Articles

- Ensure proper documentation maintained such as:
  - Lot/batch number
  - Expiration/manufacturing dates
  - Assay results
  - Formulation details- final formulation
  - Source/Manufacturer

# Test and Control Articles

- Manufactured under Good Manufacturing Practices (GMPs) or similar conditions
  - Generally applies to drug batches in pre-approval clinical studies in which the intended final formulation is used (may include GCP and GLP studies)
  - Similar:  methods for formulation, manufacturing, and testing in accordance with GMP standard but methods not fully validated or documentation completed
  - CDER's "CGMP Guidance for Phase I Investigational Drugs"

# Test and Control Articles: Medicated Feeds

- Appropriate assay methods
  - Consider risks if not fully validated before study
- Assay results should fall within approved or investigational assay limits
- Avoid contamination with other drugs during mixing process
  - In some cases, testing for last run study drug is appropriate
- Drug accountability very important

# Test and Control Article Characterization: GLP Studies (21 CFR 58.105)

- Must determine and document (for each batch) identity, strength, purity, and composition or other characteristics which define the test and control article
- Testing facility or the sponsor must document methods of synthesis, fabrication, or derivation of the test and control articles
- Test facility or sponsor must determine stability of test and control article either before or during study
- Label and store test and control articles properly
- Retain reserve samples from each batch for studies of more than 4 weeks duration

# Test and Control Article Characterization: GLP studies (21 CFR 58.105)

- Responsibility for test article characterization and stability testing may be assumed by the facility performing the study or by the study sponsor (CPG Manual 7348.808)
- If performed by the sponsor, transparency and documentation are critical
  - Document appropriate characteristics
  - Sponsor statement provided to test facility
- If performed by test facility or contributing scientist, raw data archived with rest of study data.
  - Appropriate characterization studies conducted and available for review

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# Feed and Water

- Ensure personnel understand and implement feeding practices consistent with the protocol
- Ensure data on nutrient content are collected per protocol
- Monitor for feed and water issues that could impact study outcome
  - Example:  regional variations in dietary ingredients in production drug studies
  - Manipulations of mineral levels or extreme pH in water could impact drug activity

# Feed and Water: GLP Considerations

- 58.45 provides for proper feed storage
- 58.81(b)(2) requires standard operating procedures for animal care (e.g., nutrition) - these should be followed during the study

# Feed and Water: GLP Considerations

- 58.90(g) requires periodic analysis of feed and water for interfering contaminants
- 58.120(a)(7) requires the protocol to contain a description or an identification of the diet, including specifications for acceptable levels of contaminants- ensure these levels are not exceeded

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# Concurrent Medications

- Follow pre-defined criteria in protocol
- Discussions with CVM encouraged if questions arise during study
- Record all treatments given before enrollment and during the study

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# Test Animals

- Documentation of animal source, history, and processing as appropriate
- Ensure and document inclusion and exclusion based on protocol specified parameters

# Test Animals

- Animal Accountability
  - Until end of study or investigational withdrawal time satisfied
  - Important to be able to demonstrate proper frequency of observation, explain missing data points, and follow the study conduct
- Animal Removals
  - Per protocol and exit examinations and/or necropsies performed
  - Ensure appropriate documentation, including reason

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# Control of Bias

- Randomization
  - Perform per protocol
  - May be performed centrally (by the sponsor for all sites) or individually at each study site
- Masking
  - Protect masking
  - Plan for unmasking

# Protecting Masking: Study Procedures Examples

- Number or letter vials so treatment identification not seen
- Use more labels/codes than actual number of groups
  - Example: Study with two treatment groups, may use four codes (A/B/C/D); if unequal allocation, very important to use at least three codes (A/B/C)
- Housing identification for animals should not include any indication of treatment
  - Example: Do not use a group code because will inform observers which animals received same treatment

# Protecting Masking: Plan for Unmasking

- Planned unmasking
  - Treatment failures to determine future treatment of condition
  - Pre-planned interim analysis
- Unplanned Unmasking
  - Identification of information in audit reports
- Use protocol specified procedures if masking broken
  - Document date, time, circumstances
  - Confirm for which animals/groups masking is broken
  - Notification of sponsor, CVM if appropriate

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# Data Collection and Management

- Ensure Data collection/Management plan is in place before the start of the study
- Train personnel appropriately on data quality and integrity principles
  - Quality = ALCOA (attributable, legible, contemporaneous, original, accurate)
  - Integrity = CCC (credible, corroborative, consistent)
- Error correction in accordance with protocol
- Collect all data – expected and unexpected

# Data Capture Forms

- Signatures: generally include dated observer and recorder signatures/initials if both are involved
- Transfer of all observations on a DCF to same electronic file may decrease errors during data entry

# Owner Diaries

- Primary purpose is to collect compliance and adverse event information
- Improving quality of diaries
  - Owner training
  - Use of standard terminology
  - Communication through study
- Categorization of adverse events

# What is raw data?

- GCP: "…Any original worksheets, calibration data, records, memoranda and notes of first-hand observations and activities of a study that are necessary for the reconstruction and evaluation of the study..."
  - Facsimile transmissions and transcribed data are not considered raw data
- 21 CFR 58.3(k): "…laboratory worksheets, records, memoranda, notes, or exact copies thereof, that are the result of original observations and activities of a non-clinical laboratory study and are necessary for the reconstruction and evaluation of the report of that study…"

# Data Quality Principles

The raw data are:

- Attributable- can be traced (signature/initials and date) to the individual(s) observing and recording the data.
- Legible- readable and recorded in a permanent medium. If changes are made to original entries, the changes are made appropriately
- Contemporaneous- recorded at the time of the observation.
- Original- the first recording of the data.
- Accurate- true and complete observations

# Data Integrity Principles

- Credible:  Based on real and reliable facts
- Corroborative:  Backed up by evidence
- Consistent:  Demonstrate the required attributes consistently

# Units of Measure:
# Standard International units vs. US units

- Collect data in units consistent with equipment
- Use of units of measure that are familiar to investigator may reduce errors
- Consistency within study or study sites
- For US submissions, talk to CVM prior to submission

# Data derivations and conversions

- Should not be performed during data collection/recording
  - Potential for computation errors
  - Example: unit conversion or addition of several variables into composite
- Should be completed after the data freezing/lock

# Rounding

- Follow protocol specified procedures
- Precision should be recorded in accordance to equipment being used
- Everyone should follow the same process of how to record a number
  - Particularly an issue with multi-site studies
- Rounding methods during dose administration
  - Should be specified in protocol
  - Primarily injectable drugs, but an issue for other formulations as well (topicals)
  - Consider animal weight, dose, drug concentration
  - Generally rounding should ensure within 10% of target dose

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# Amendments and Deviations

- Protocol amendment: “A written change or modification of the study protocol effected prior to the implementation of the protocol or execution of the changed or modified task.” (GCP)
- Protocol deviation: “A departure from the procedures stated in the study protocol.” (GCP)
- (GLP)- Any changes in or revisions to the approved protocol must be documented along with the reasoning
- Special considerations for MUMS studies supported by grants

# Deviations

- Ensure all are well-documented and evaluated for their impact on the study with relation to pivotal variables
  - Sponsor should make final assessment
- May be found by monitor
- Should have clear guidelines for notification of sponsor during the study

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# Adverse Events

- GCP : “Any observation in animals that is unfavorable and unintended and occurs after the use of a veterinary product or investigational veterinary product, whether or not considered to be product related.”
- Ensure appropriate people are notified (including CVM if necessary, per 21 CFR 511.1(b)(8)(ii))

# Adverse Events

- Training of personnel in identification and documentation is important
- Report AEs as recorded, prior to reclassification or categorization

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# Quality Oversight

- Independent QA unit required by GLP regulations
- QA including use of a monitor recommended by GCP
- Sponsor ultimately responsible for all the data
  - Different ways to accomplish this

# Monitoring

- Good monitoring may help sponsors catch issues early
- Should keep records of communication at the site
- Sites with high enrollment or more deviations should be monitored more frequently

# Documentation of GLP compliance or non-compliance

- QA unit (21 CFR 58.35)
  - Monitors to assure conformance with the regulations and informs study director and TFM of problems
- Study Director (21 CFR 58.33)
  - Assures all GLP regulations are followed
  - Notes and documents corrective action for unforeseen circumstances that may impact quality and integrity of the data
- TFM (21 CFR 58.31)
  - Assures that deviations from regulations are communicated to study director and corrective action taken and documented

# Documentation of GLP compliance or non-compliance

- Pre-planned non-compliance
  - Described and justified in protocol
  - Document how GLPs followed in spirit
- Non-compliance identified during study
  - Describe how problem corrected
  - Impact on establishment's operations, study conduct, and data integrity

# GLP compliance documentation also useful for:

- Compliance statement (from sponsor) required as described in 21 CFR 514.1
  - Documentation and transparency during the study assists the sponsor in compiling the statement

# GLP compliance documentation also useful for:

- Discussions with FDA inspectors
  - Not all findings of non-compliance are significant enough to be listed on an FDA 483
  - Findings should not be listed on the FDA 483 if in the opinion of the field investigator (ref CPG 7348.808):
    - The findings are problems that have been observed and corrected by the firm through its internal procedures.
    - The findings are minor and are one-time occurrences that have no impact on the firm's operations, study conduct, or data integrity.

# Summary

- The quality of data is enhanced through careful selection of site and investigator/study director
- Training of personnel is imperative
- Carefully follow the protocol and regulations
- Use good data collection and management practices
- Monitor and document

# Building Quality Data - Reporting and Submitting

Center for Veterinary Medicine

June 4 and 6, 2013

# Reporting and Submitting Data

- Reporting
  - Compiling the data
    - Reviewing the data
    - Preparing the electronic file
    - Analyzing the data
  - Preparing the report
- Submitting

# Compiling: Reviewing Data

- Sources of raw data include
  - Paper records

    Typically DCFs, chromatograms, photographs, planned/unexpected observations, adverse events, other information
  - Electronic records

    Directly recorded electronic data using a Part 11 compliant system, including data audit trail

# Compiling:  Reviewing Data

- Raw data are reviewed and verified for correct recording, e.g. signatures, electronic forms
- Data typically reviewed for validity and adherence to ALCOA principles
  - May use any effective method available

# Compiling:  Preparing the e-File

- The electronic raw data file (e-File) is the electronic dataset(s) provided to CVM for analysis and review
- The e-File consists of electronic copies of data transcribed from paper records and original electronic records

# Compiling: Preparing the e-File

- Keep file size manageable
  - Maximum permissible file size – 100 MB
    - eSubmitter submission – requirement
    - “paper” (other) submission – strong preference
  - Divide data into multiple files in a logical structure
    - Clinical chemistry, hematology, or reproductive variables, feed related observations from production drug study

# Compiling: Preparing the e-File

- Create self-contained files
  - Permit independent evaluation without need for additional files
  - Include identifying variables in each file, e.g. treatment, sex, block, site
  - Inclusion of same variables (except identifying variables) in multiple files is discouraged

# Compiling:  Preparing the e-File

- File(s) should contain all recorded data
  - Data can be excluded from analyses using programming
  - If corrections need to be made after data file lock-down, those can be made with programming as well

# Compiling: Preparing the e-File

- Follow process detailed in the protocol for freezing and locking data files
  - Freeze: May be performed multiple times and does not indicate data are in the final form. Data are not unmasked.
  - Lock: No further changes can be made. Performed after review, query, resolution of questions but before unmasking.

# Analyzing Data

- Data Exclusion Meeting
  - At the discretion of the sponsor
    - Is not a presubmission conference meeting - please request as OO (ONADE other) meeting
    - Held before data are unmasked
  - Discuss exclusion of subject or individual data values
  - No decision is final because all information is not yet available to CVM

# Analyzing Data

- Analysis: any assessment of results
  - Whether with or without summaries or statistical tools
- Performed on frozen/locked datasets
- Changes to analysis strategies
  - May discuss with CVM before submission
  - Documented as protocol amendment or deviation

# Reporting Data: Tell the Story

- Present the study actions, results, and conclusions in a logical format that best tells the story
  - Can CVM reconstruct the study?
  - Be expansive in scope
  - Do individual and tabular values trace to raw data?
  - Can be helpful to follow the study protocol

# Report Components

- Executive Summary – hit the high points
- Material and Methods – how did you do it
- Results – what did you find
- Conclusions – what does it mean

# Executive Summary

- Include brief description of study design
  - Treatments, number of animals/sites, drug dosage
- Discuss major results of study
  - Expected and unexpected
- Highlight significant conclusions
  - Do results support purpose of study?

# Materials and Methods

- Drug administration
  - Dose calculations to confirm correct levels
- Bias control
  - Masking, randomization
- Adverse event documentation
  - Use clear standardized terminology for AEs

# Materials and Methods

- Description of subjective study processes
  - Define any scoring/coding systems used
    - Pain, depression, success criteria
- Provide equations for calculations and transformations
- Summary of analysis
  - Details may be in statistical report

# Results - Content Points

- Discuss all of the data
  - Brevity/omission leads to unnecessary questions
- Group AEs appropriately
  - Discuss observed trends
  - Reflect authors' assessment of causality
  - Sponsor has final submission recommendation
  - CVM final assessment determination on evaluation
- Protocol amendments and deviations
  - Describe impact on data collection and results

# Results – Presentation Points

- Use summaries and statistical analyses to guide discussion of results
- Report appropriate means and associated P-values
  - Covariate-adjusted least squares means
- Consider tabular/graphic presentation to aid interpretation
- Make appropriate connections to supporting reports

# Conclusions

- Do the results support the hypothesis or purpose of the study?
- Provide a persuasive scientific argument for the conclusions that can be drawn
  - Particularly important for multiple studies

# Report and Associated Documents

- Final Study Report
- Appendices
  - Raw data
  - Contributing scientist reports
  - Study protocol, as amended
  - Important SOPs

# Sponsor's GLP Compliance Statement (GCS) – The issue

- There has been a long-standing ambiguity, within both CVM and the regulated industry, as to the nature and necessity of seemingly duplicative requirements regarding assessments of the quality of non-clinical studies.

# Sponsor's GCS – What is it?

- Statement required of the sponsor for each GLP study submitted to CVM in support of an application
  - "With respect to each nonclinical laboratory study contained in the application, either a statement that the study was conducted in compliance with … [the GLP regulations]…, or if the study was not conducted in compliance, a brief statement of the reason for the non-compliance." (21 CFR 514.1(b)(12)(iii))

# Sponsor's GCS – What is the intent?

- The intent of the regulation is ensure that sponsors are aware of the quality of non-clinical data they are submitting.
- The requirement has existed since the GLP regulations and the associated changes to existing regulations were finalized in 1978.

# Sponsor's GCS – What is the intent?

- "… The revisions [of existing regulations] highlight the fact that although studies not conducted in compliance with the regulations may continue to be submitted to FDA, **the burden of establishing that the non-compliance did not affect the quality of the data submitted is on the person submitting the noncomplying study**."
  - From comment #253 in the preamble to the final GLP regulations, 43 FR 60013, 1978

# Sponsor's GCS – Is it important?

- Consider the actions that can occur in its absence:
  - Is considered an untrue statement in an application (21 CFR 514.15(c))
  - Is grounds to refuse to file an application (21 CFR 514.110(b)(8))
  - Is grounds to refuse to approve an application (21 CFR 514.111(a)(11))

# Sponsor's GCS – Why now?

- CVM has not consistently required, nor have sponsors consistently provided, these statements as part of their submitted applications.
- CVM's flexibility to help sponsors efficiently meet our requirements is increasing.
- There is increasing use of "non-traditional" testing facilities where knowledge of, and experience with, the GLP regulations may not be adequate.

# Sponsor's GCS – Why now?

- The current level of ambiguity within CVM and industry, the use of 'inexperienced' testing facilities, and a faster tempo to the drug approval process has created an environment where it is no longer possible to assure that the quality of non-clinical data has not been adversely impacted.
- Returning to the use of the GCS will rightly place the burden of data quality back on the sponsors.

# Sponsor's GCS – These aren't it.

- The similar statement required to be included in the final report of a nonclinical study
  - "a description of all circumstances that may affect the quality or integrity of the study." (21 CFR 58.185(a)(9))

# Sponsor's GCS – These aren't it.

- The statement required to be prepared by the QAU and to be included with the final study report (21 CFR 58.35(b)(7) and 58.185(a)14))
  - This statement contains the dates QA inspections were performed and reported to test facility management and the study director.

# Sponsor's GCS – Model Statement

- Part 1: "I have personally inspected the final study report (including all raw data) and other study-associated information for compliance with the GLP regulations found at 21 CFR part 58. Based on my review, my assessment is that this non clinical laboratory study (was/was not) conducted in full compliance with the regulations found in part 58."

# Sponsor's GCS – Model Statement

- Part 2: *(Include the following paragraph where non-compliance is noted.)* "My review of this information revealed non-compliance with the following sections of the GLP regulations: (provide a list of those section(s) where non-compliance was noted and a brief statement of the reason for the non-compliance)."
- This statement should be signed by the individual performing the review.

# Organization of Submission

- Cover letter and Form FDA 356v or eSubmitter responses
- Table of contents for the entire submission
- Regulatory summary
  - Draws conclusions using information from all studies included in submission
- Compliance statements
- Final study report(s) with all appendices

# Submitting Electronic Files

- File type choice critical to CVM
  - These files are becoming our official records
  - Selected to provide the greatest chance of being readable or usable in the future with minimal effort
    - Non-proprietary format
    - Less dependent on software version
    - Accessible using free software
  - Preserves files for future use by sponsor or CVM

# Submitting Electronic Files

- PDF – Portable Document Format
  - Used for text and image files
    - Study reports, scanned DCFs, ReadMe files, log and output files
- XML – Extensible Markup Language
  - Used for data files and program files
    - Non-proprietary (i.e., not Microsoft's) version required
- XPT – SAS Transport (XPORT)
  - Can be used for data files; prefer XML
- CVM Biostatistics can assist in converting data files

# Submitting Electronic Files

- XPT limitations
  - Must use XPORT not CPORT (proprietary) files
  - Variable names are limited to 8 characters
  - Need SAS Universal Viewer (free software) or SAS software to read files

# Submitting Electronic Files

- XML
  - More generous variable name length
  - Files can be read using Excel, Notepad, or other text file readers

# Electronic File Specifications

Resource for electronic file creation for both eSubmitter and “paper” (other) submissions:

http://www.fda.gov/downloads/ForIndustry/FDAeSubmitter/UCM332980.pdf

# Submitting Electronic Files

- Electronic (eSubmitter) submissions
  - Only PDF, XML, and XPT files are accepted
- “Paper” (other) submissions
  - CVM strongly recommends the use of PDF, XML, and XPT files
  - Contact CVM if considering other formats

# eSubmitter File Organization

- File names
  - Do not use special characters (e.g., #, *%)*
  - Limit path length by limiting the number of subdirectories used
  - Indicate data or program file if possible
- Maximum permissible file size is 100 MB

# eSubmitter File Organization

Submit text files as PDF files

- Organize physical files with logical breaks
- Content of each file should be easy to describe
- PDF file must be subjected to optical character recognition (OCR'd) to allow bookmarks and text searches
- Bookmark files

# eSubmitter File Organization

- Submit analysis programs as XML files
  - For SAS, simply save/rename files having SAS extensions with the XML extension

# eSubmitter File Organization

- SAS code to generate non-proprietary XML files

```
libname in 'file location';
libname out xml 'file location\filename1.xml';
data out.dataset1; set in.filename; run;
```

- SAS code to generate XPT files

```
libname in 'file location';
libname out xport 'file location\filename1.xpt';
data out.filename1; set in.filename; run;
```

# eSubmitter File Organization

- SAS code to read non-proprietary XML files

```
libname in xml 'file location\filename.xml';
data filename1; set in.dataset1; run;
```

- SAS code to read XPT files

```
libname in xport 'file location\filename.xpt';
data filename1; set in.dataset1; run;
```

# All Submissions

- Include a “Read Me” text file
  - Identifies all data and analysis program file names
  - Describes the purpose of each file

# All Submissions

- Include a “Read Me” text file
  - For each data file, describe contents
    - Truncated variable name if used (BWT)
    - Complete variable name (body weight)
    - Units of measure (kg)
  - Identify data files used in each analysis program

# All Submissions

- Internally document analysis programs sufficiently to explain data manipulation and specialized procedures
  - When excluding data, identify the reason and person directing the exclusion
  - Identify the purpose for inclusion of other program files

# All Submissions

- Analysis Programs
  - Because we will be using XPT or XML files to view and analyze your data, we recommend that you do the same
  - Include in the submission all sub-programs used to perform statistical tests, file conversions, and summarize data.
  - Simple programs are the best.

# Summary: Reporting and Submitting

- Verify raw data is captured accurately in e-file(s)
- Create complete/accurate final study report
- Include sponsor's GCS for GLP studies
- Submit compliant PDF, XML, and XPT files

# Question and Answer Session

- Reminder that the questions and answers from this session have been incorporated into the Questions and Answers document.

# Webinar Closing Remarks